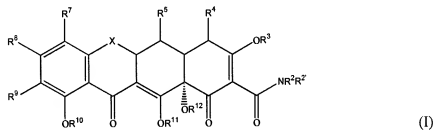


# Amendments to the Claims

This listing of claims will replace all prior versions and listings of claims in the application:

1. **(Currently Amended)** A method for treating or preventing malaria in a subject, comprising administering to said subject an effective amount of a substituted tetracycline compound of formula I or a pharmaceutically acceptable salt thereof:



wherein:

- X is CR<sup>6'</sup>R<sup>6</sup>;
- R<sup>2</sup> and R<sup>2'</sup> are each hydrogen;
- R<sup>4'</sup> and R<sup>4''</sup> are each alkyl;
- R<sup>4</sup> is NR<sup>4'</sup>R<sup>4''</sup>;
- R<sup>3</sup>, R<sup>11</sup> and R<sup>12</sup> are each hydrogen;
- R<sup>10</sup> is hydrogen;
- R<sup>5</sup> is hydroxyl, hydrogen or thiol;
- R<sup>6</sup> and R<sup>6'</sup> are independently hydrogen, hydroxyl, thiol or alkyl;
- R<sup>7</sup> is substituted or unsubstituted furanyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted thienyl or substituted or unsubstituted benzothienyl;
- R<sup>9</sup> is hydrogen; and
- R<sup>8</sup> is hydrogen; ~~and pharmaceutically acceptable salts thereof~~; such that malaria is treated or prevented in said subject.

- 2. **(Canceled)**
- 3. **(Canceled)**
- 4. **(Previously Presented)** The method of claim 1, wherein R<sup>5</sup>, R<sup>6</sup>, and R<sup>6'</sup> are each hydrogen.

5 - 28. (Canceled)

29. (Currently Amended) The method of claim 1, wherein  $R^7$  is substituted furanyl or substituted thienyl.

30. (Previously Presented) The method of claim 29, wherein  $R^7$  is substituted with halogen, alkoxy, amino, acyl, alkyl, nitro, formyl, amido, alkenyl, alkynyl, or aryl.

31. (Previously Presented) The method of claim 30, wherein  $R^7$  is substituted with alkoxy and further wherein said alkoxy is methoxy, ethoxy, propoxy, methylene dioxy, or ethylene dioxy.

32. (Previously Presented) The method of claim 30, wherein  $R^7$  is substituted with alkyl and further wherein said alkyl is substituted or unsubstituted methyl, ethyl, propyl, butyl or pentyl.

33. (Previously Presented) The method of claim 32, wherein said substituted methyl, ethyl, propyl, butyl or pentyl is substituted with an amino, carbocyclic or heterocyclic group.

34. (Previously Presented) The method of claim 30, wherein  $R^7$  is substituted with acyl and further wherein said acyl is acetyl.

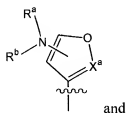
35. (Previously Presented) The method of claim 1, wherein  $R^7$  is substituted or unsubstituted benzofuranyl or substituted or unsubstituted benzothienyl.

36. (Previously Presented) The method of claim 1, wherein  $R^7$  is unsubstituted thienyl or unsubstituted furanyl.

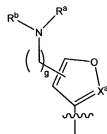
37 - 41. (Canceled)

42. (Previously Presented) The method of claim 29, wherein said substituent comprises an ionizable nitrogen atom.

43. (Previously Presented) The method of claim 1, wherein  $R^7$  is selected from the group consisting of:



and



wherein:

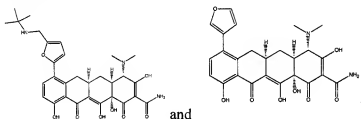
$R^a$  and  $R^b$  are each independently hydrogen, halogen, alkyl, alkenyl, alkynyl, aryl, aralkyl, alkoxy, or heterocyclic;

$g$  is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20; and

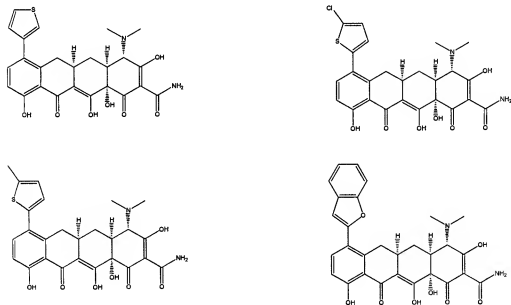
$X^9$  is substituted carbon.

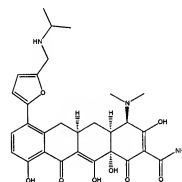
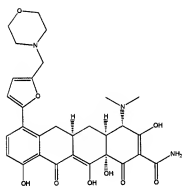
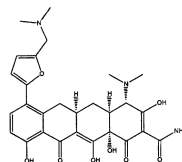
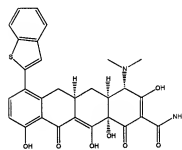
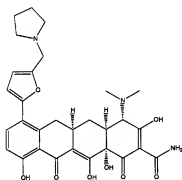
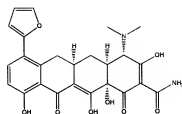
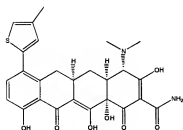
44 – 48. (Canceled)

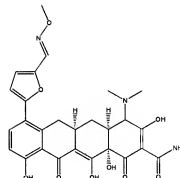
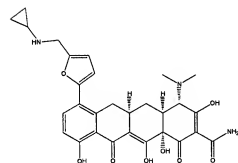
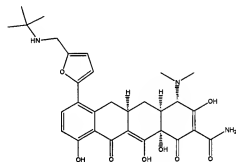
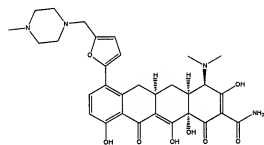
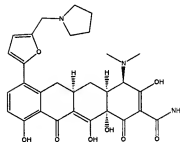
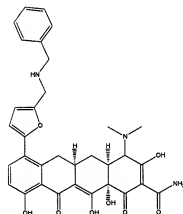
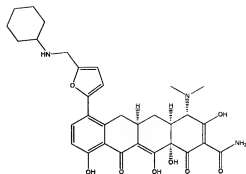
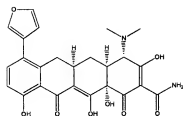
49. (Previously Presented) The method of claim 1, wherein said compound is selected from the group consisting of:

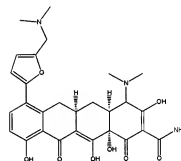
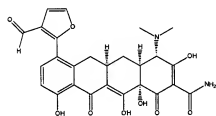
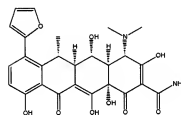
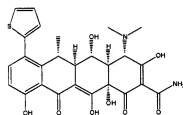
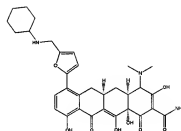
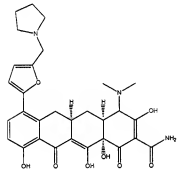
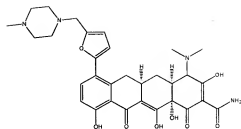
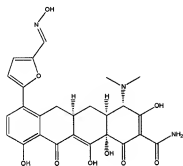


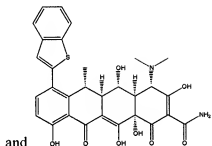
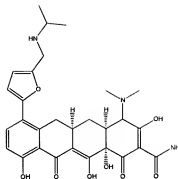
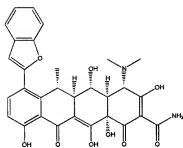
50. (Previously Presented) The method of claim 1, wherein said compound is selected from the group consisting of:











and

51. **(Original)** The method of claim 1, wherein said subject is a human.
52. **(Previously Presented)** The method of claim 1, wherein said substituted tetracycline compound has anti-gram positive microbial activity.
53. **(Previously Presented)** The method of claim 52, wherein said anti-gram positive microbial activity is greater than about 0.05  $\mu\text{g/ml}$ .
54. **(Previously Presented)** The method of claim 53, wherein said anti-gram positive microbial activity is greater than about 5  $\mu\text{g/ml}$ .
55. **(Previously Presented)** The method of claim 1, wherein said substituted tetracycline compound is non-antibacterial.
56. **(Original)** The method of claim 1, wherein said substituted tetracycline compound has a cytotoxicity of 25  $\mu\text{g/ml}$  or greater.
57. **(Original)** The method of claim 1, wherein said substituted tetracycline compound has a MIC of 150 nM or less.
58. **(Original)** The method of claim 57, wherein said substituted tetracycline compound has a MIC of 50 nM or less.
59. **(Original)** The method of claim 58, wherein said substituted tetracycline compound has a MIC of 10 nM or less.

60. **(Currently Amended)** The method of claim 59, wherein said substituted tetracycline compound has a MIC [[or]] of 5 nM or less.

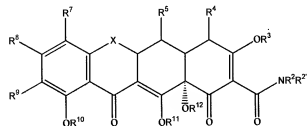
61. **(Original)** The method of claim 1, wherein said malaria is caused by a plasmodium protozoan selected from the group consisting of: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*.

62. **(Currently Amended)** The method of claim 1, wherein said malaria is resistant to one or more anti-malarial compounds selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine[[.]] and 1,16-hexadecamethylenebis(N-methylpyrrolidinium) dibromide.

63 – 65. **(Canceled)**

66. **(Currently Amended)** The method of claim 1, further comprising administering an anti-malarial compound selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide[[.]] and combinations thereof.

67. **(Currently Amended)** A method for increasing the antimalarial activity of an antimalarial compound, comprising administering said antimalarial compound in combination with an effective amount of a substituted tetracycline compound, such that the antimalarial activity of said antimalarial compound is increased, wherein said tetracycline compound is of formula I or a pharmaceutically acceptable salt thereof:



(I)

wherein:



X is  $\text{CR}^6\text{R}^6$ ;

$\text{R}^2$  and  $\text{R}^{2'}$  are each hydrogen;

$\text{R}^{4'}$  and  $\text{R}^{4''}$  are each alkyl;

$\text{R}^4$  is  $\text{NR}^{4'}\text{R}^{4''}$ ;

$\text{R}^3$ ,  $\text{R}^{11}$  and  $\text{R}^{12}$  are each hydrogen;

$\text{R}^{10}$  is hydrogen;

$\text{R}^5$  is hydroxyl, hydrogen or thiol;

$\text{R}^6$  and  $\text{R}^6$  are independently hydrogen, hydroxyl, thiol or alkyl;

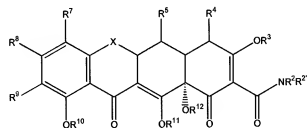
$\text{R}^7$  is substituted or unsubstituted furanyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted thienyl or substituted or unsubstituted benzothienyl;

$\text{R}^9$  is hydrogen; and

$\text{R}^8$  is hydrogen; and ~~pharmaceutically acceptable salts thereof.~~

68. **(Currently Amended)** The method of claim 67, wherein said anti-malarial compound is selected from the group consisting of: proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, ampyroquine, sulphonamides, artemisinin, arteflene, artemether, artesunate, primaquine, pyronaridine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide[[.]] and combinations thereof.

69. **(Currently Amended)** A method for preventing malaria in a mammal, comprising administering to said mammal an effective amount of a substituted tetracycline compound, such that malaria is prevented in said mammal, wherein said tetracycline compound is of formula I or a pharmaceutically acceptable salt thereof:



(I)

wherein:

X is  $\text{CR}^6\text{R}^6$ ;

$R^2$  and  $R^{2'}$  are each hydrogen;

$R^{4'}$  and  $R^{4''}$  are each alkyl;

$R^4$  is  $NR^4'R^{4''}$ ;

$R^3$ ,  $R^{11}$  and  $R^{12}$  are each hydrogen;

$R^{10}$  is hydrogen;

$R^5$  is hydroxyl, hydrogen or thiol;

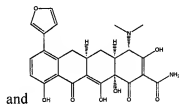
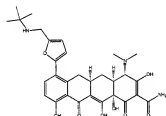
$R^6$  and  $R^{6'}$  are independently hydrogen, hydroxyl, thiol or alkyl;

$R^7$  is substituted or unsubstituted furanyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted thienyl or substituted or unsubstituted benzothienyl;

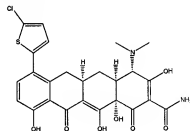
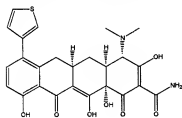
$R^9$  is hydrogen; and

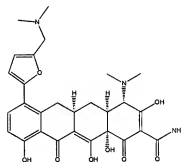
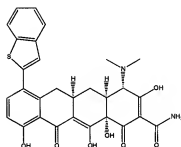
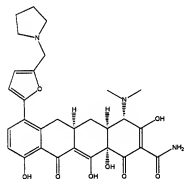
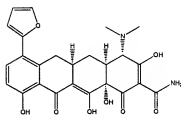
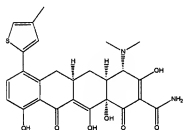
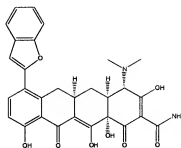
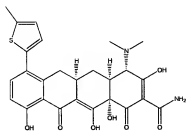
$R^8$  is hydrogen; ~~and pharmaceutically acceptable salts thereof.~~

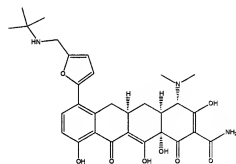
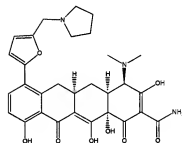
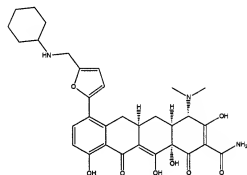
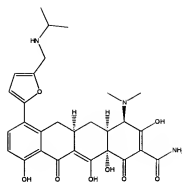
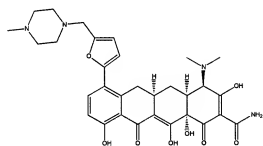
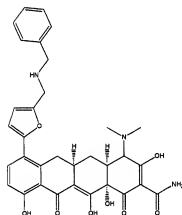
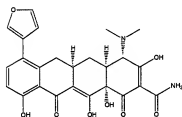
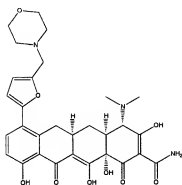
70. **(Previously Presented)** The method of claim 69, wherein said substituted tetracycline compound is selected from the group consisting of:

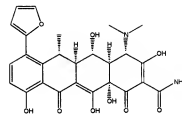
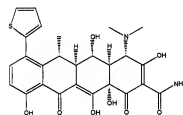
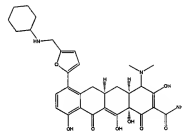
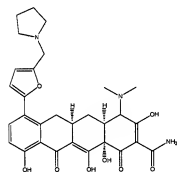
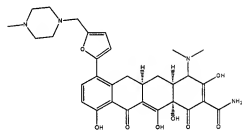
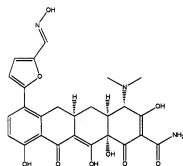
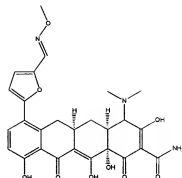
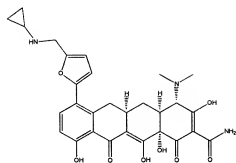


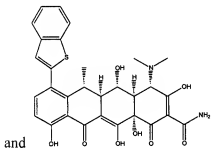
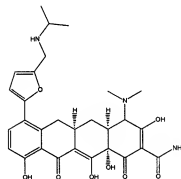
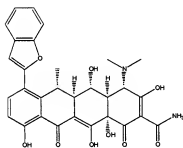
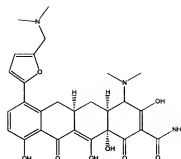
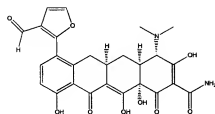
71. **(Previously Presented)** The method of claim 69, wherein said substituted tetracycline compound is selected from the group consisting of:











and

72. **(Previously Presented)** The method of claim 69, wherein said substituted tetracycline compound is non-antibacterial.

73. **(Previously Presented)** The method of claim 69, wherein said substituted tetracycline compound has anti-gram positive microbial activity.

74. **(Previously Presented)** The method of claim 73, wherein said anti-gram positive microbial activity is greater than about 0.05  $\mu\text{g/ml}$ .

75. **(Previously Presented)** The method of claim 74, wherein said anti-gram positive microbial activity is greater than about 5  $\mu\text{g/ml}$ .

76. **(Original)** The method of claim 75, wherein said substituted tetracycline compound has a cytotoxicity of 25  $\mu\text{g/ml}$  or greater.

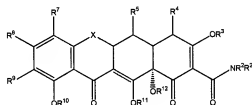
77. **(Previously Presented)** The method of claim 69, wherein said substituted tetracycline compound has a MIC of 150 nM or less.

78. **(Original)** The method of claim 77, wherein said substituted tetracycline compound has a MIC of 50 nM or less.

79. **(Original)** The method of claim 78, wherein said substituted tetracycline compound has a MIC of 10 nM or less.

80. **(Currently Amended)** The method of claim 79, wherein said substituted tetracycline compound has a MIC [[or]] of 5 nM or less.

81. **(Currently Amended)** A pharmaceutical composition comprising an effective amount of a substituted tetracycline compound to treat malaria in a mammal and a pharmaceutically acceptable carrier, wherein said tetracycline compound is of formula I or a pharmaceutically acceptable salt thereof:



wherein:

X is CR<sup>6'</sup>R<sup>6</sup>;

R<sup>2</sup> and R<sup>2'</sup> are each hydrogen;

R<sup>4'</sup> and R<sup>4''</sup> are each alkyl;

R<sup>4</sup> is NR<sup>4'</sup>R<sup>4''</sup>;

R<sup>3</sup>, R<sup>11</sup> and R<sup>12</sup> are each hydrogen;

R<sup>10</sup> is hydrogen;

R<sup>5</sup> is hydroxyl, hydrogen or thiol;

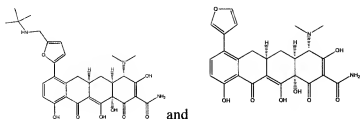
R<sup>6</sup> and R<sup>6'</sup> are independently hydrogen, hydroxyl, thiol or alkyl;

R<sup>7</sup> is substituted or unsubstituted furanyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted thienyl or substituted or unsubstituted benzothienyl;

R<sup>9</sup> is hydrogen; and

R<sup>8</sup> is hydrogen; ~~and pharmaceutically acceptable salts thereof.~~

82. **(Previously Presented)** The pharmaceutical composition of claim 81, wherein said substituted tetracycline compound is selected from the group consisting of:



83. (Canceled)

84. (Currently Amended) The pharmaceutical composition of claim 81, further comprising a ~~secondary agent~~ anti-malarial compound.

85. (Currently Amended) The pharmaceutical composition of claim 84, wherein the ~~secondary agent~~ anti-malarial compound is selected from the group consisting of proguanil, chlorproguanil, trimethoprim, chloroquine, mefloquine, lumefantrine, atovaquone, pyrimethamine-sulfadoxine, pyrimethamine-dapsone, halofantrine, quinine, quinidine, amodiaquine, amopyroquine, sulphonamides, artemisinin, arteflenc, artemether, artesunate, primaquine, 1,16-hexadecamethylenebis(N-methylpyrrolidinium)dibromide and pyronaridine.

86. (Canceled)

87. (Canceled)